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A MODEL STUDY FOR THE SYNTHESIS OF THE HEXAHYDROBENZOFURAN FRAGMENT OF THE MILBEMYCINS AND AVERMECTINS.

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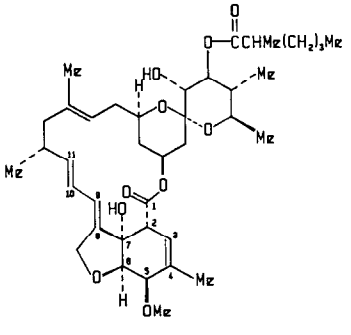
Summary: An INOC based approach to the hexahydrobenzofuran portion of the milbemycins and the avermectins is described in which a high level of π-facial selectivity has been observed in a six-membered ring forming reaction.

The milbemycins are a structurally intriguing class of macrolide antibiotics produced in submerged cultures of Streptomyces hygroscopicus subsp. aureolacrimosus. These compounds are active against acarus, harmful agricultural and horticultural insects such as aphids and larvae of insects of the order Lepidoptera. Thirteen milbemycins have been isolated from this species of Streptomyces.[1]

While two total syntheses of milbemycin β_3 have been reported,[2] no total synthesis has yet been published of any of the more complex members of this family. Several reports[3] on the preparation of the spiroketal portions of these more complex milbemycins (and the structurally related compounds, the avermectins[4]) have, however, appeared. Additionally, one approach to the unusual hexahydrobenzofuran fragment of the avermectins which utilizes nitrile oxide chemistry has been published.[5]



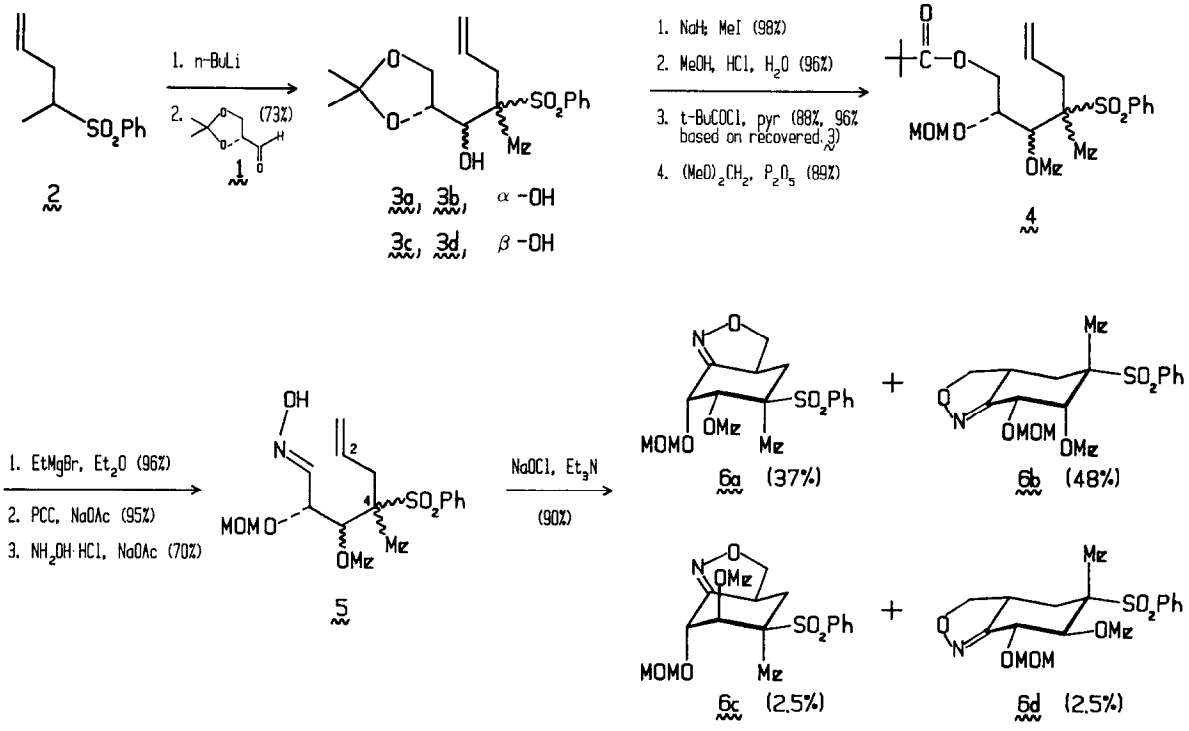
Milbemycin α_6

In this Letter we disclose an approach to the hexahydrobenzofuran fragment which also makes use of the INOC reaction and which starts from optically active glyceraldehyde acetonide. While the S isomer of the aldehyde is required for the preparation of this fragment of correct absolute stereochemistry, our preliminary studies were nonetheless carried out with the R isomer because of

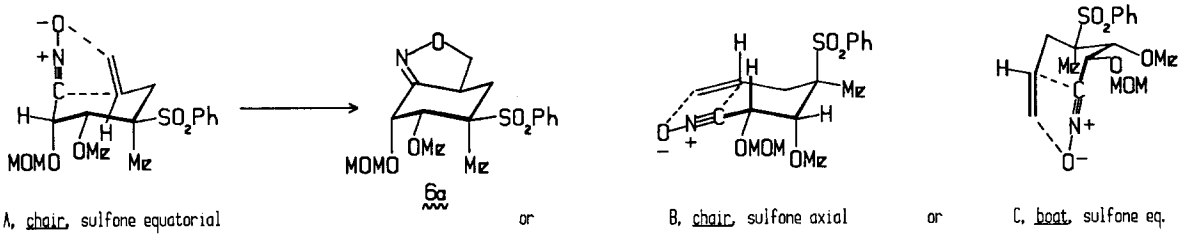
its greater accessibility.[6]

First, a condensation reaction was carried out between the sulfone stabilized anion of **2**[7] and the aldehyde **1**. While a mixture of diastereomers resulted, the stereochemistry of the new hydroxyl bearing center was found (vide infra) to correspond primarily to addition via a Felkin-like transition state[8] (**3a**+**3b** : **3c**+**3d** = 16:1).

This mixture of products was O-methylated, and transformed to the oximes **5**. An INOC cyclization was then brought about by treating these oximes with sodium hypochlorite. The resulting isoxazolines could be separated readily, and the two major products **6a** and **6b** crystallized for X-ray analysis. These X-ray structures revealed the stereochemistry of C_5 relative to C_6, thus confirming the Felkin-like nature of the original condensation reaction. Moreover, the X-ray structures in combination with a close examination of molecular models suggested that the INOC reaction must proceed through a chair-like transition state **A** with the sterically demanding phenyl sulfone group assuming the pseudo-equatorial position.[9] Attack on the other π-face of the olefin would require reaction through a higher energy chair-like transition state **B** with the sulfone group occupying an axial position (or alternatively a boat-like transition state **C** with the bulky sulfone group equatorial). The two minor isomers **6c** and **6d** formed in this reaction presumably reflect the small amount of anti-Felkin product generated in the initial sulfone condensation. Some spectral evidence for these latter assignments derives from an analysis of the H_5-H_6 coupling constants (3 Hz for **6c** and 9.5 Hz for **6d**). The stereochemistry present in the starting oxime at C_4 thus effectively controls the stereochemical outcome at C_2 in the course of the nitrile oxide cycloaddition reaction.

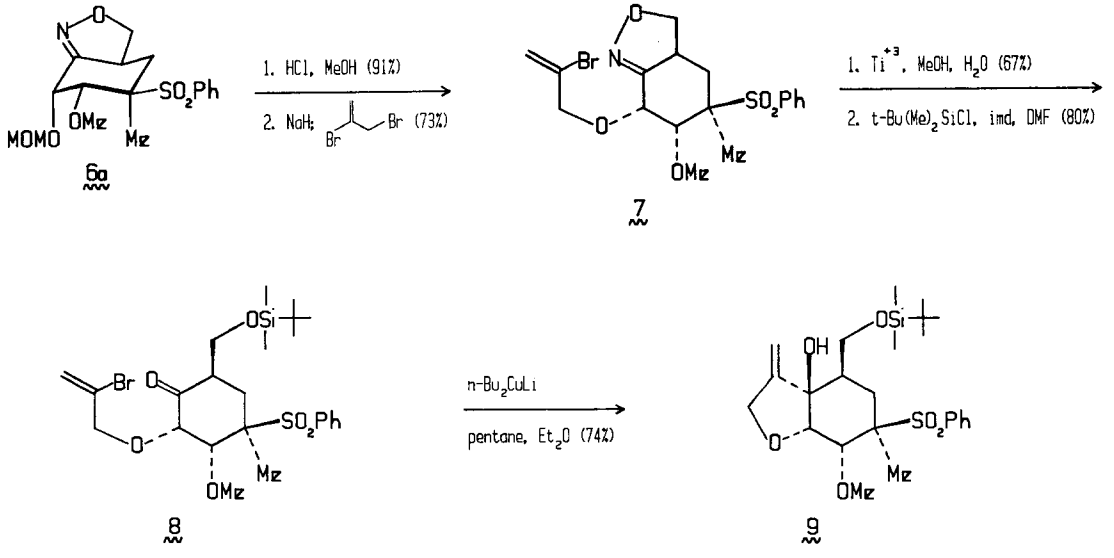


Possible Transition States for One of the Diastereomers of 5



To append the tetrahydrofuran ring to **6a**, the MOM group was removed and replaced by a 2-bromo-2-propenyl group. The isoxazoline ring was now cleaved using Torsell's conditions (Ti^{+3}, MeOH, H_2O),[10] and the newly freed alcohol was protected by silylation. Conditions devised by Corey during his gibberellic acid[11] work served to complete our model study, for on simply exposing **8** to di-n-butylcopper lithium, the desired reduced furan ring system **9** was generated. The stereochemistry of the tertiary alcohol center must be as drawn, for the chain tethered nucleophile occupies an axial position, and it is thus incapable of attacking the other face of the carbonyl group. The use of isomer **6b** in this same scheme should also give rise to a product possessing the desired stereochemistry at C_7 due to the well known tendency of such small ring forming processes to lead to cis-fused products.[12,13]

While the phenylsulfonyl group could potentially be used to install the required degree of unsaturation into **9**, we have made few experiments in this direction. The information garnered during this model study has led us to consider a modified scheme in which a 1,3-diene rather than an alkene is employed in the INOC reaction so that the required degree of unsaturation is present at the start of the synthesis.



The present study does reveal the possibility of achieving high levels of diastereoselection in six-membered ring forming INOC reactions. The principles of acyclic stereoselection can thus be melded with dipolar cycloaddition chemistry to provide cyclic structures of high stereochemical purity.

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13. **6a**: ^{1}H NMR ($CDCl_3$) δ 7.87-7.47 (m, 5 H), 5.00 (d, 1 H, J = 4.5 Hz), 4.64-4.51 (m, 3 H), 4.06 (dd, 1 H, J= 8.0, 8.0 Hz), 3.91 (d, 1 H, J = 4.5 Hz), 3.67-3.51 (m, 1 H), 3.32 (s, 3 H), 3.30 (s, 3 H), 2.35 (dd, 1 H, J = 13.5, 6.1 Hz), 2.00 (dd, 1 H, J = 13.5, 13.5 Hz), 1.58 (s, 3 H). **9**: ^{1}H NMR ($CDCl_3$) δ 7.91-7.47 (m, 5 H), 5.21 (s, 1 H), 5.14 (br s, 1 H), 5.08 (br s, 1 H), 4.43 (m, 2 H), 4.27 (dd, 1 H, J = 10.4, 2.3 Hz), 4.15 (d, 1 H, J = 4.0 Hz), 4.00 (d, 1 H, J = 4.0 Hz), 3.66 (dd, 1 H, J = 10.4, 2.0 Hz), 3.30 (s, 3 H), 2.65 (dd, 1 H, J = 3.3, 3.3 Hz), 1.74 (m, 2 H), 1.54 (s, 3 H), 0.94 (s, 9 H), 0.12 (s, 6 H).

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